```
     (FILE 'HOME' ENTERED AT 09:02:29 ON 21 MAR 2002)

     FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, LIFESCI, WPIDS, USPATFULL' ENTERED
     AT 09:03:54 ON 21 MAR 2002
L1            15 S EGP-2(25W)LOCAL?
L2             5 DUP REM L1 (10 DUPLICATES REMOVED)
L3            23 S EGP-2(25W)NORMAL
L4             6 DUP REM L3 (17 DUPLICATES REMOVED)
L5            40 S EGP-2(25W)EPITHEL?
L6            19 DUP REM L5 (21 DUPLICATES REMOVED)
L7           725 S (EGP-2 OR EP-CAM OR 17-1A OR CO17-1A) (25W)(CANCER OR TUMOR O
L8           574 S (EGP-2 OR EP-CAM OR 17-1A OR CO17-1A) (15W)(CANCER OR TUMOR O
L9           646 S (EGP-2 OR EP-CAM OR 17-1A OR CO17-1A OR KSA) (15W)(CANCER OR
L10          173 S L9 AND (TREAT? OR ADMINI? OR MODUL?)(15W)(CANCER OR TUMOR OR
L11           81 S L10 AND (TREAT? OR ADMINI? OR MODUL?)(15W)(ANTIBOD?)
L12           50 DUP REM L11 (31 DUPLICATES REMOVED)
L13           35 S MUC-1(25W)COLON
L14           24 S L13 AND COLON (25W)(CANCER OR TUMOR OR TUMOUR)
L15            8 S L14 AND (TREAT? OR ADMINI? OR MODUL?)(25W)(CANCER OR TUMOR OR
L16           15 DUP REM L14 (9 DUPLICATES REMOVED)

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L3 ANSWER 20 OF 21 CAPLUS COPYRIGHT 2002 ACS
AN 1995:508513 CAPLUS
DN 122:288268
TI The immunogenicity of MUC1 peptides and fusion protein
AU Apostolopoulos, V.; Pietersz, G. A.; Xing, P.-X.; Lees, C. J.; Michael, M.; Bishop, J.; McKenzie, I. F. C.
CS Austin Research Institute, Austin Hospital, Studley Road, Heidelberg, Vic., 3084, Australia
SO Cancer Lett. (Shannon, Irel.) (1995), 90(1), 21-6
CODEN: CALEDQ; ISSN: 0304-3835
DT Journal; General Review
LA English
AB A review and discussion with 22 refs. Mucin1 (MUC1) is highly expressed in **breast cancer**, has an ubiquitous distribution and, due to altered glycosylation, peptides within the VNTR are exposed. These peptides are the target for anti-MUC1 antibodies, which give a differential reaction on cancer compared with normal tissue. The amino acids, APDTR or adjacent amino acids, are highly immunogenic in mice for antibody prodn. (after immunization with either **breast cancer** cells, human milk fat globule (HMFG) or the VNTR peptide). In addn., human studies show that this region of the MUC1 VNTR functions as target epitopes for cytotoxic T cells. We have performed preclin. and clin. studies to examine the immune responses to MUC1 in mice and humans: (a) MUC1+ 3T3 or P815+ 3T3 cells in syngeneic mice are rejected, with the generation of both cytotoxic T lymphocyte (CTL) and DTH responses and a weak antibody response; this type of immunity gives rise to total resistance to re-challenge with high doses of these tumors; (b) immunization with peptides (VNTR .times. 2), a fusion protein (VNTR.times.5), or HMFG leads to no CTLs, DTH, good antibody prodn. and weak tumor protection (to 106 cells, but not 5.times.106 cells) (possibly a TH2 type response); (c) immunization with mannan-fusion protein (MFP) gives rise to good protection (resistance to 50.times.106 cells), CTL and DTH responses and weak antibody responses (possibly a TH1 type response, similar in magnitude to that obtained after tumor rejection); (d) established tumors can be rapidly rejected by delayed **treatment** of MFP; (e) the CTL responses are MHC restricted (in contrast to the human studies); (f) APDTR appears not to be the T cell reactive epitope in mice. On the basis of these findings, two clin. trials are in progress: (a) VNTR .times. 2 (diphtheria toxoid) which gives rise to some T cell proliferation, DTH and antibody responses in some patients and (b) an MFP trial. The ability to alter the immune response towards cellular immunity with mannan or to humoral immunity with peptides, allows the immune response to be selectively manipulated.
AB A review and discussion with 22 refs. Mucin1 (MUC1) is highly expressed in **breast cancer**, has an ubiquitous distribution and, due to altered glycosylation, peptides within the VNTR are exposed. These peptides are the target for anti-MUC1 antibodies, which give a differential reaction on cancer compared with normal tissue. The amino acids, APDTR or adjacent amino acids, are highly immunogenic in mice for antibody prodn. (after immunization with either **breast cancer** cells, human milk fat globule (HMFG) or the VNTR peptide). In addn., human studies show that this region of the MUC1 VNTR functions as target epitopes for cytotoxic T cells. We have performed preclin. and clin. studies to examine the immune responses to MUC1 in mice and humans: (a) MUC1+ 3T3 or P815+ 3T3 cells in syngeneic mice are rejected, with the generation of both cytotoxic T lymphocyte (CTL) and DTH responses and a weak antibody response; this type of immunity gives rise to total resistance to re-challenge with high doses of these tumors; (b) immunization with peptides (VNTR .times. 2), a fusion protein (VNTR.times.5), or HMFG leads to no CTLs, DTH, good antibody prodn. and weak tumor protection (to 106 cells, but not 5.times.106 cells) (possibly a TH2 type response); (c) immunization with mannan-fusion protein (MFP) gives rise to good protection (resistance to 50.times.106 cells), CTL and

L7 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2002 ACS
AN 2001:401949 CAPLUS
DN 135:165763
TI The epithelial glycoprotein 2 (EGP-2) promoter-driven epithelial-specific expression of EGP-2 in transgenic mice: a new model to study carcinoma-directed immunotherapy
AU McLaughlin, Pamela M. J.; Harmsen, Martin C.; Dokter, Wim H. A.; Kroesen, Bart-Jan; Van der Molen, Henk; Brinker, Marja G. L.; Hollema, Harry; Ruiters, Marcel H. J.; Buys, Charles H. C. M.; De Leij, Lou F. M. H.
CS Department of Pathology and Laboratory Medicine, section of Medical Biology, University Hospital Groningen, Groningen, 9713 GZ, Neth.
SO Cancer Research (2001), 61(10), 4105-4111
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
AB The human pancarcinoma-assocd. epithelial glycoprotein-2 (EGP-2), a Mr 38,000 transmembrane antigen also known as 17-1A or Ep-CAM, is commonly used for targeted immunotherapy of carcinomas because it is strongly expressed by most carcinomas. EGP-2 is, however, also expressed in most normal epithelia. To evaluate anti-EGP-2-directed treatment-assocd. effects on tumors and on EGP-2-pos. normal tissue, we generated EGP-2-expressing transgenic mice. A 55-kb DNA fragment consisting of the 14-kb genomic coding sequence of the human EGP-2 gene with .apprx.10-kb-upstream and .apprx.31-kb-downstream sequences was isolated and used to direct EGP-2 expression in an epithelium-specific manner. In the EGP-2 transgenic mice, EGP-2 appeared to be specifically expressed in all of those epithelial tissues that also express EGP-2 in humans, whereas all of the other tissues were neg. The specific in vivo localization of the i.v. administered anti-EGP-2 monoclonal antibody MOC31 was studied in EGP-2-pos. and -neg. tumors induced s.c. in this EGP-2 transgenic mouse model. Immunohistochem. anal. showed specific localization of MOC31 in the EGP-2-pos. tumors but not in the EGP-2-neg. tumors. No anti-EGP-2 monoclonal antibody localization was obsd. in any of the EGP-2-pos. normal mouse tissues, which indicated a limited in vivo accessibility. In conclusion, an EGP-2 transgenic mouse model has been generated that expresses the EGP-2 antigen as in humans and, therefore, can serve as a model to evaluate the efficacy and safety of a variety of anti-EGP-2-based immunotherapeutic modalities in both tumors and normal tissue.
RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 5 MEDLINE DUPLICATE 1
AN 2000192069 MEDLINE
DN 20192069 PubMed ID: 10725458
TI A rapid and versatile method for harnessing scFv antibody fragments with various biological effector functions.
AU Helfrich W; Haisma H J; Magdolen V; Luther T; Bom V J; Westra J; van der Hoeven R; Kroesen B J; Molema G; de Leij L
CS Groningen University Institute for Drug Exploration (GUIDE) at the University Hospital Groningen, Department of Pathology and Laboratory Medicine, Medical Biology Branch, Hanzeplein 1, 9713 GZ, Groningen, The Netherlands.. w.helfrich@med.rug.nl
SO JOURNAL OF IMMUNOLOGICAL METHODS, (2000 Apr 3) 237 (1-2) 131-45.
Journal code: IFE; 1305440. ISSN: 0022-1759.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200005
ED Entered STN: 20000512
Last Updated on STN: 20000512
Entered Medline: 20000501
AB A versatile expression vector is described for the rapid construction and

evaluation of bispecific scFvs and scFv-based fusion proteins. An important feature of this vector is the presence of two multiple cloning sites (MCS) separated by an in frame linker sequence. The first MCS was specifically designed to contain unique SfiI and NotI restriction enzyme sites that can be used for directional and in frame insertion of scFvs (or potentially any molecule) selected from established phage-display systems. Using this new vector, a functional bs-(scFv)(2) (2C11-MOC31) was constructed for retargeted T-cell cytotoxicity towards **EGP2** positive **tumor** cells. The vector was also used for grafting of a number of promising biological effector principles onto scFv MOC31, including the prodrug converting enzyme cytosine deaminase, the anti-angiogenic factor angiostatin, and the thrombogenic molecule tissue factor. We aimed at producing biologically active fusion proteins by directing them through the endoplasmic reticulum-based protein folding machinery of eukaryotic cells (COS-7) using a kappa light chain leader, thereby taking advantage of the associated quality control mechanisms that allow only fully folded and processed fusion proteins to be secreted into the medium. Supernatants derived from fusion protein transfected COS-7 cells, which were transiently transfected at low transfection rates, were directly assayed for the biological and/or targeting activity of the excreted fusion proteins without any prior purification steps. This procedure might help to identify those fusion proteins that have favourable characteristics like stability and biological activity in the presence of serum and at low protein concentrations. Targeted delivery of all effector principles was subsequently assessed in an in vitro model system. The method we devised is both rapid and versatile and can be useful to construct and identify series of new chimeric proteins with enhanced therapeutic potential in human cancer therapy.

most efficient. Out of 41 serum samples from **breast-cancer** patients, 11 showed elevated levels of the 9H8 epitope, and several sera also showed elevated levels of the cancer-associated carbohydrate epitopes sialyl-Lewis a and sialyl-Lewis x. By the use of **antibodies** specific for the **MUC1** apoprotein (Ma552 and HMFG-2) it could be shown that these epitopes were attached to the **MUC1** apoprotein in at least 4 of the cases. By combining antibodies specific to 9H8, sialyl-Lewis a and sialyl-Lewis x in. . .

L3 ANSWER 19 OF 21 CAPLUS COPYRIGHT 2002 ACS
AN 1997:92341 CAPLUS
DN 126:156186
TI Characterization of a new **breast cancer**-associated antigen and its relationship to MUC1 and TAG-72 antigens
AU Harada, Yuko; Ohuchi, Noriaki; Masuko, Takashi; Funaki, Yoshihito; Mori, Shozo; Satomi, Susumu; Hashimoto, Yoshiyuki
CS The Second Department of Surgery, Tohoku University School of Medicine, Sendai, 980-77, Japan
SO Tohoku J. Exp. Med. (1996), 180(3), 273-288
CODEN: TJEMAO; ISSN: 0040-8727
PB Tohoku University Medical Press
DT Journal
LA English
AB We have characterized a new tumor-assocd. antigen defined by monoclonal antibody (MAb) generated against HMA-1 **breast cancer** cell line. MAb AM-1 was selected based on its preferential reactivity to **breast cancer** cells vs. to normal or benign epithelial cells by immunofluorescence and immunohistochem. assays of cultured, or fresh specimens. AM-1 demonstrated strong reactivity to **breast cancer** cell lines including HMA-1, YMB-1-E, YMB-1 and MDA-MB-231 in flow cytometry. In immunopptn., AM-1 recognized high mol. wt. components of 160-210 kDa and >370 kDa. Reactivity with HMA-1 cells was diminished markedly when **treated** by heat, protease or periodate, suggesting that the antigenic epitope is composed of carbohydrates and peptides. Enzyme digestion of pptd. antigens demonstrated that the antigen contains O-linked and N-linked carbohydrates with neuraminic acid structures. Furthermore, binding inhibition and sandwich ELISA assays using MAbs reactive with known **breast cancer**-assocd. antigens and synthetic MUCI core peptide (PDTRPAPGSTAPPAHGVTSAPDTR) demonstrated that the antigen is distinct from CEA, TAG-72 or MUC1, while the antigen conjoins with MUC1 and TAG-72 as a trimer form in HMA-1 cells. These results suggest that AM-1 recognizes a novel glycoprotein which is abundant in **breast cancer**, and may be utilized in the management of **breast cancer** patients.
TI Characterization of a new **breast cancer**-associated antigen and its relationship to MUC1 and TAG-72 antigens
AB We have characterized a new tumor-assocd. antigen defined by monoclonal antibody (MAb) generated against HMA-1 **breast cancer** cell line. MAb AM-1 was selected based on its preferential reactivity to **breast cancer** cells vs. to normal or benign epithelial cells by immunofluorescence and immunohistochem. assays of cultured, or fresh specimens. AM-1 demonstrated strong reactivity to **breast cancer** cell lines including HMA-1, YMB-1-E, YMB-1 and MDA-MB-231 in flow cytometry. In immunopptn., AM-1 recognized high mol. wt. components of 160-210 kDa and >370 kDa. Reactivity with HMA-1 cells was diminished markedly when **treated** by heat, protease or periodate, suggesting that the antigenic epitope is composed of carbohydrates and peptides. Enzyme digestion of pptd. antigens demonstrated that the antigen contains O-linked and N-linked carbohydrates with neuraminic acid structures. Furthermore, binding inhibition and sandwich ELISA assays using MAbs reactive with known **breast cancer**-assocd. antigens and synthetic MUCI core peptide (PDTRPAPGSTAPPAHGVTSAPDTR) demonstrated that the antigen is distinct from CEA, TAG-72 or MUC1, while the antigen conjoins with MUC1 and TAG-72 as a trimer form in HMA-1 cells.

These results suggest that AM-1 recognizes a novel glycoprotein which is abundant in **breast cancer**, and may be utilized in the management of **breast cancer** patients.

ST **breast cancer** antigen AM1 glycoprotein

IT Antigens
RL: BOC (Biological occurrence); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(AM-1; characterization of a new **breast cancer**-assocd. antigen and its relationship to MUC1 and TAG-72 antigens)

IT Antigens
RL: BOC (Biological occurrence); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(MUC1; characterization of a new **breast cancer**-assocd. antigen and its relationship to MUC1 and TAG-72 antigens)

IT Breast tumors
(characterization of a new **breast cancer**-assocd. antigen and its relationship to MUC1 and TAG-72 antigens)

IT Monoclonal **antibodies**
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(characterization of a new **breast cancer**-assocd. antigen and its relationship to **MUC1** and TAG-72 antigens)

IT Tumor-associated glycoprotein 72
RL: BOC (Biological occurrence); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(characterization of a new **breast cancer**-assocd. antigen and its relationship to MUC1 and TAG-72 antigens)

1998196936 MEDLINE

DN 98196936 PubMed ID: 9537586

TI Construction and characterization of a bispecific diabody for retargeting T cells to human carcinomas.

AU Helfrich W; Kroesen B J; Roovers R C; Westers L; Molema G; Hoogenboom H R; de Leij L

CS GUIDE, University Hospital, Department of Clinical Immunology, Groningen, The Netherlands.

SO INTERNATIONAL JOURNAL OF CANCER, (1998 Apr 13) 76 (2) 232-9.
Journal code: GQU; 0042124. ISSN: 0020-7136.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199804

ED Entered STN: 19980422
Last Updated on STN: 19980422
Entered Medline: 19980416

AB We describe the construction of a recombinant bispecific antibody fragment in the diabody format with specificity for both the well-established human pancarcinoma associated target antigen EGP2 (epithelial glycoprotein 2, also known as the C017-1A antigen or KSA) and the CD3epsilon chain of human TCR/CD3 complex. The murine anti-EGP2 (MOC31) single chain variable fragment (scFv) and the humanized anti-CD3 (Ucht1v9) scFv were cast into a diabody format (designated Dia5v9) using a short 5 amino acid Gly-Ser linker between immunoglobulin heavy-chain and light-chain variable domains. Purification of the poly-histidine tagged Dia5v9 was achieved from extracts of protease deficient Escherichia coli by IMAC chromatography. The Dia5v9 diabody showed strong binding to both **EGP2** and CD3 in transfected cells. The in vitro efficacy of Dia5v9 in mediating **tumor** cell lysis by interleukin-2 activated human T cells appeared to be similar to that of the hybrid-hybridoma-derived BsF(ab')2 Bis1 (anti-EGP2/anti-CD3) in a standard 4-hr 51Cr-release assay. This small and partially humanized recombinant bispecific antibody fragment may be valuable for T-cell-based immunotherapeutical treatment protocols, retargeting activated peripheral blood T lymphocytes to lyse various human carcinomas in vivo.

17 - 1#

E_2 - CH1

L17
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43
40
34

DTH responses and weak antibody responses (possibly a TH1 type response, similar in magnitude to that obtained after tumor rejection); (d) established tumors can be rapidly rejected by delayed **treatment** of MFP; (e) the CTL responses are MHC restricted (in contrast to the human studies); (f) APDTR appears not to be the T cell reactive epitope in mice. On the basis of these findings, two clin. trials are in progress: (a) VNTR .times. 2 (diphtheria toxoid) which gives rise to some T cell proliferation, DTH and antibody responses in some patients and (b) an MFP trial. The ability to alter the immune response towards cellular immunity with mannan or to humoral immunity with peptides, allows the immune response to be selectively manipulated.

IT **Antibodies**
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(immunogenicity of **MUC1** peptides and fusion protein)

=>

=> d l3 10 12 14 15 16 18 19 bib ab kwic

L3 ANSWER 10 OF 21 CAPLUS COPYRIGHT 2002 ACS
AN 1999:528990 CAPLUS
DN 131:169287
TI Specific antibodies against mammary tumor-associated mucin, method for production and use
IN Bastert, Gunther; Kaul, Sepp
PA Germany
SO PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9940881	A2	19990819	WO 1999-EP941	19990212
	WO 9940881	A3	19991125		
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9935966	A1	19990830	AU 1999-35966	19990212
	EP 1056472	A2	20001206	EP 1999-917815	19990212
	R: AT, BE, CH, DE, FR, GB, IT, LI, NL, SE				
	JP 2002502621	T2	20020129	JP 2000-531139	19990212
PRAI	EP 1998-102529	A	19980213		
	WO 1999-EP941	W	19990212		

AB An immunol. active polypeptide which specifically binds to the carbohydrate structure of the MUC1 tandem repeat from carcinoma cells, wherein (a) the quotient between the affinity of the said polypeptide for a 200 to 440 kDa glycoprotein fraction from tumor cell-contg. ascites of **breast cancer** patients and for native MUC1 antigen (400 to 440 kDa) from normal cells is 100:1 or more, (b) the polypeptide does not bind to nonglycosylated MUC1 antigen, and (c) the binding of the polypeptide to the said 200 to 440 kDa glycoprotein fraction changes by 10 % or less if the glycoprotein fraction was **treated** with neuraminidase to cleave N-terminal neuraminic acids, or with formalin, is specific for MUC1 and is useful in the diagnosis and therapy of **breast cancer**.

AB An immunol. active polypeptide which specifically binds to the carbohydrate structure of the MUC1 tandem repeat from carcinoma cells, wherein (a) the quotient between the affinity of the said polypeptide for a 200 to 440 kDa glycoprotein fraction from tumor cell-contg. ascites of **breast cancer** patients and for native MUC1 antigen (400 to 440 kDa) from normal cells is 100:1 or more, (b) the polypeptide does not bind to nonglycosylated MUC1 antigen, and (c) the binding of the polypeptide to the said 200 to 440 kDa glycoprotein fraction changes by 10 % or less if the glycoprotein fraction was **treated** with neuraminidase to cleave N-terminal neuraminic acids, or with formalin, is specific for MUC1 and is useful in the diagnosis and therapy of **breast cancer**.

ST monoclonal **antibody MUC1** antigen breast carcinoma

IT Glycoproteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(200,000-440,000 mol. wt.; specific **antibodies** against mammary tumor-assocd. mucin **MUC1** for immunotherapy of **breast cancer**)

IT Animal cell line
(DSM ATCC 2328 and 2329; specific **antibodies** against mammary tumor-assocd. mucin **MUC1** for immunotherapy of **breast cancer**)
IT Immunoglobulins
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(G1; specific **antibodies** against mammary tumor-assocd. mucin **MUC1** for immunotherapy of **breast cancer**)
IT Agglutinins and Lectins
RL: BUU (Biological use, unclassified); DEV (Device component use); BIOL (Biological study); USES (Uses)
(affinity chromatog.; specific **antibodies** against mammary tumor-assocd. mucin **MUC1** for immunotherapy of **breast cancer**)
IT Mammary gland
(carcinoma; specific **antibodies** against mammary tumor-assocd. mucin **MUC1** for immunotherapy of **breast cancer**)
IT Toxins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(conjugates; specific **antibodies** against mammary tumor-assocd. mucin **MUC1** for immunotherapy of **breast cancer**)
IT Toxins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cytotoxins, conjugate; specific **antibodies** against mammary tumor-assocd. mucin **MUC1** for immunotherapy of **breast cancer**)
IT Mucins
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(episialins; specific **antibodies** against mammary tumor-assocd. mucin **MUC1** for immunotherapy of **breast cancer**)
IT Wheat
(germ, agglutinin; specific **antibodies** against mammary tumor-assocd. mucin **MUC1** for immunotherapy of **breast cancer**)
IT Affinity chromatography
(lectin; specific **antibodies** against mammary tumor-assocd. mucin **MUC1** for immunotherapy of **breast cancer**)
IT **Antibodies**
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(monoclonal; specific **antibodies** against mammary tumor-assocd. mucin **MUC1** for immunotherapy of **breast cancer**)
IT Mammary gland
(neoplasm; specific **antibodies** against mammary tumor-assocd. mucin **MUC1** for immunotherapy of **breast cancer**)
IT Antiserums
Ascites
Body fluid
Carcinoma
Eukaryote (Eukaryotae)
Gel permeation chromatography
Immunotherapy
Pleural fluid
Prokaryote
T cell (lymphocyte)
(specific **antibodies** against mammary tumor-assocd. mucin

MUC1 for immunotherapy of **breast cancer**)

IT **Antibodies**
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(specific **antibodies** against mammary tumor-assocd. mucin **MUC1** for immunotherapy of **breast cancer**)

IT Carbohydrates, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(specific **antibodies** against mammary tumor-assocd. mucin **MUC1** for immunotherapy of **breast cancer**)

IT Immunoglobulins
RL: REM (Removal or disposal); PROC (Process)
(specific **antibodies** against mammary tumor-assocd. mucin **MUC1** for immunotherapy of **breast cancer**)

IT Peptides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(specific **antibodies** against mammary tumor-assocd. mucin **MUC1** for immunotherapy of **breast cancer**)

IT Proteins, general, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(specific **antibodies** against mammary tumor-assocd. mucin **MUC1** for immunotherapy of **breast cancer**)

IT Repetitive DNA
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(tandem, MUC1; specific **antibodies** against mammary tumor-assocd. mucin **MUC1** for immunotherapy of **breast cancer**)

IT Agglutinins and Lectins
RL: BUU (Biological use, unclassified); DEV (Device component use); BIOL (Biological study); USES (Uses)
(wheat germ; specific **antibodies** against mammary tumor-assocd. mucin **MUC1** for immunotherapy of **breast cancer**)

IT 50-00-0, Formaldehyde, biological studies 9001-67-6, Neuraminidase
RL: BAC (Biological activity or effector, except adverse); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(specific **antibodies** against mammary tumor-assocd. mucin **MUC1** for immunotherapy of **breast cancer**)

IT 7512-17-6, N-Acetyl-glucosamine
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(specific **antibodies** against mammary tumor-assocd. mucin **MUC1** for immunotherapy of **breast cancer**)

IT 9012-36-6, Sepharose 98726-62-6, Superose 6
RL: BUU (Biological use, unclassified); DEV (Device component use); BIOL (Biological study); USES (Uses)
(specific **antibodies** against mammary tumor-assocd. mucin **MUC1** for immunotherapy of **breast cancer**)

IT 114-04-5D, Neuraminic acid, derivs.
RL: REM (Removal or disposal); PROC (Process)
(specific **antibodies** against mammary tumor-assocd. mucin **MUC1** for immunotherapy of **breast cancer**)

L3 ANSWER 12 OF 21 MEDLINE
AN 2000050713 MEDLINE
DN 20050713 PubMed ID: 10583575
TI Expression of MUC1 and MUC2 mucin gene products in Barrett's metaplasia, dysplasia and adenocarcinoma: an immunopathological study with clinical correlation.
AU Chinyama C N; Marshall R E; Owen W J; Mason R C; Kothari D; Wilkinson M L; Sanderson J D
CS Department of Histopathology, Guy's and St. Thomas' Hospital, London, UK.. c.chinyama@umds.ac.uk

SO HISTOPATHOLOGY, (1999 Dec) 35 (6) 517-24.
Journal code: GB4; 7704136. ISSN: 0309-0167.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200001
ED Entered STN: 20000204
Last Updated on STN: 20000204
Entered Medline: 20000127
AB AIMS: Changes in the histochemical characteristics of the surface epithelial mucins is the hallmark of Barrett's metaplasia. The study investigated the pattern of expression of MUC1 and MUC2 mucin gene products in Barrett's metaplasia, dysplasia and adenocarcinoma as possible indicators of increased malignant potential. METHODS AND RESULTS: Tissue sections from 51 patients with Barrett's intestinal metaplasia, nine with dysplasia (three indefinite) and 28 resected adenocarcinomas were stained with monoclonal **antibodies** to **MUC1** and MUC2. The majority of the patients were men (70/88, 80%) who were **treated** over a period of 3 years. None of the patients with dysplasia or carcinoma were under surveillance at the time of presentation. All 51 biopsies with Barrett's metaplasia expressed MUC2 and MUC1 was consistently absent. Neither MUC1 or MUC2 were expressed in the dysplastic epithelium whether in its pure form (6/6) or when associated with carcinoma (26/28) ($P < 0.005$). Three biopsies which were initially classified as high-grade dysplasia expressed MUC1 and these turned out to be carcinomas on further investigations. MUC1 was also expressed in 12/28 (43%) of the adenocarcinomas and majority of these were poorly differentiated stage 3 tumours ($P < 0.05$). MUC2 was only positive in mucin-secreting carcinomas (4/28; 14%) irrespective of the tumour stage. CONCLUSION: Despite the large number of patients with Barrett's metaplasia and carcinoma, very few patients presented with dysplasia, implying that Barrett's oesophagus is a silent disease in the community presenting late as carcinoma. The study has demonstrated aberrant expression of MUC2 (an intestinal mucin) in Barrett's metaplasia and this expression is lost when the cells become dysplastic. The lack of MUC1 in dysplastic epithelium and its expression in carcinoma could be utilized as a marker which could differentiate dysplasia from carcinoma in mucosal biopsies. Furthermore, expression of MUC1 in advanced stage oesophageal cancers (as in **breast cancer**) suggests an unfavourable prognosis.
AB . . . from 51 patients with Barrett's intestinal metaplasia, nine with dysplasia (three indefinite) and 28 resected adenocarcinomas were stained with monoclonal **antibodies** to **MUC1** and MUC2. The majority of the patients were men (70/88, 80%) who were **treated** over a period of 3 years. None of the patients with dysplasia or carcinoma were under surveillance at the time. . . which could differentiate dysplasia from carcinoma in mucosal biopsies. Furthermore, expression of MUC1 in advanced stage oesophageal cancers (as in **breast cancer**) suggests an unfavourable prognosis.

L3 ANSWER 14 OF 21 CAPLUS COPYRIGHT 2002 ACS
AN 1998:327865 CAPLUS
DN 129:121311
TI An enzyme-linked immunosorbent assay for the measurement of circulating **antibodies** to polymorphic epithelial mucin (**MUC1**)
AU Von Mensdorff-Pouilly, Silvia; Gourevitch, Maia M.; Kenemans, Peter; Verstraeten, Albert A.; Van Kamp, Gerard J.; Kok, Astrid; Van Uffelen, Kees; Snijdewint, Frank G. M.; Paul, Marinus A.; Meijer, Sybren; Hilgers, Joseph
CS Departments of Obstetrics and Gynaecology, Academic Hospital Vrije Universiteit, Amsterdam, NL-1081 HV, Neth.
SO Tumor Biol. (1998), 19(3), 186-195
CODEN: TUMBEA; ISSN: 1010-4283
PB S. Karger AG

DT Journal
LA English
AB About one-third of breast and ovarian carcinoma patients have circulating **antibodies** reactive with polymorphic epithelial mucin (**MUC1**), either free or bound to immune complexes. While the presence of these immune complexes has prognostic significance in **breast cancer** patients, the significance of free MUC1 antibodies is less clear. The objective here was to develop a reliable assay for the accurate detn. of circulating free **antibodies** to **MUC1**. The authors developed an ELISA (PEM.CIg) employing a 60 mer peptide (a triple tandem repeat sequence of the MUC1 peptide core) conjugated to bovine serum albumin and peroxidase-labeled antihuman IgG or IgM antibodies. The assay was standardized and its anal. performance evaluated. A total of 492 serum samples were obtained from 40 healthy men, 201 healthy women (including 55 women without a history of pregnancy and 45 pregnant women), and (before primary **treatment**) 62 benign breast tumor patients and 190 **breast cancer** patients. MUC1 serum levels were detd. with com. CA 15-3 tests. Circulating **antibodies** to **MUC1** are present both in healthy subjects and in **breast cancer** patients. The within- and between-assay coeffs. of variation were, resp., 2 and 12% for the IgG detns. and 1.2 and 3% for the IgM detns. Correlation coeffs. for serially dild. serum samples ranged from 0.9998 to 0.9920 for IgG and from 0.9996 to 0.9818 for IgM detns. The reactivity of serum samples was partially blocked by the addn. of various MUC1 peptides and by MUC1 mucin. The inhibiting effect of modified 60 mer peptides suggests the presence of antibodies directed to >1 epitope. The PEM.CIg assay is a reliable ELISA for measuring free MUC1 antibodies in serum. In addn., the assay may become a useful tool for vaccine therapy monitoring.
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ST ELISA circulating **antibody** epithelial mucin **MUC1**
IT Blood analysis
Breast tumors
(ELISA for measurement of circulating **antibodies** to polymorphic epithelial mucin **MUC1**)
IT MUC1 mucin

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ELISA for measurement of circulating **antibodies** to polymorphic epithelial mucin **MUC1**)

IT Autoantibodies
RL: ANT (Analyte); ANST (Analytical study)
(circulating; ELISA for measurement of circulating **antibodies** to polymorphic epithelial mucin **MUC1**)

L3 ANSWER 15 OF 21 MEDLINE DUPLICATE 4
AN 1998084012 MEDLINE
DN 98084012 PubMed ID: 9422094
TI Effect of desialylation on binding, affinity, and specificity of 56 monoclonal **antibodies** against **MUC1** mucin.
AU Dai J; Allard W J; Davis G; Yeung K K
CS Business Group Diagnostics, Bayer Corp., Tarrytown, N.Y. 10591, USA.
SO TUMOUR BIOLOGY, (1998) 19 Suppl 1 100-10.
Journal code: TUB; 8409922. ISSN: 0289-5447.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199801
ED Entered STN: 19980130
Last Updated on STN: 19980130
Entered Medline: 19980121
AB We evaluated 56 monoclonal **antibodies** (MAbs), submitted to the ISOBM TD-4 Workshop, for changes in binding following desialylation of the **MUC1** molecule and for epitope specificity. **Antibody** binding of MAbs was assayed by an ELISA method using microtiter plates coated with the **MUC1** mucin obtained from supernatants of the ZR75-1 cell line. The MUC1 mucin was desialylated directly on the plate by **treatment** with neuraminidase. For each MAb, binding to untreated mucin was compared over a range of antibody concentrations. The concentration at which binding was half-maximal (K50) was determined for all **antibodies** whose binding reached saturation in the assay. Results showed that K50 values for MAb binding to untreated **MUC1** mucin varied from 10(-10) to 10(-6) M. These data suggest that MAbs to MUC1 mucin bind with a broad range of intrinsic affinities. Desialylation was found to have variable effects on antibody binding, in that binding was either increased, decreased, or unchanged. No relationship was found between the apparent affinities for untreated mucin and changes in binding following desialylation. Among the 56 Workshop MAbs, 33 were found reactive with synthetic peptides which mimic the MUC1 tandem repeat. We determined the epitope specificity of the 33 MAbs by competitive binding using 10 amino acid peptides corresponding to various regions of the 20-amino acid tandem repeat domain of MUC1. All antibodies which recognized epitopes in the 1-10 amino acid region of the tandem repeat showed increased binding to desialylated mucin. **Antibodies** to other peptide epitopes showed no consistent pattern of change in binding following desialylation. Our results suggest that sialic acid residues on the **MUC1** mucin may contribute either positively or negatively to antibody binding. In addition, our results suggest that improved antibody selection methods could provide MAbs with improved selectivity for cancer-derived mucin compared with mucin from normal tissues. This could form the basis of improved biomarker assays for **breast cancer**.
TI Effect of desialylation on binding, affinity, and specificity of 56 monoclonal **antibodies** against **MUC1** mucin.
AB We evaluated 56 monoclonal **antibodies** (MAbs), submitted to the ISOBM TD-4 Workshop, for changes in binding following desialylation of the **MUC1** molecule and for epitope specificity. **Antibody** binding of MAbs was assayed by an ELISA method using microtiter plates coated with the **MUC1** mucin obtained from supernatants of the ZR75-1 cell line. The MUC1 mucin was desialylated directly on the plate by

treatment with neuraminidase. For each MAb, binding to untreated mucin was compared over a range of antibody concentrations. The concentration at which binding was half-maximal (K50) was determined for all **antibodies** whose binding reached saturation in the assay. Results showed that K50 values for MAb binding to untreated **MUC1** mucin varied from 10(-10) to 10(-6) M. These data suggest that MAbs to MUC1 mucin bind with a broad range. . . antibodies which recognized epitopes in the 1-10 amino acid region of the tandem repeat showed increased binding to desialylated mucin. **Antibodies** to other peptide epitopes showed no consistent pattern of change in binding following desialylation. Our results suggest that sialic acid residues on the **MUC1** mucin may contribute either positively or negatively to antibody binding. In addition, our results suggest that improved antibody selection methods. . . selectivity for cancer-derived mucin compared with mucin from normal tissues. This could form the basis of improved biomarker assays for **breast cancer**.

L3 ANSWER 16 OF 21 MEDLINE DUPLICATE 5
AN 1998084011 MEDLINE
DN 98084011 PubMed ID: 9422093
TI Immunohistochemical characterization of a panel of 56 antibodies with normal human small intestine, colon, and breast tissues.
AU Cao Y; Karsten U; Hilgers J
CS Max Delbruck Centre for Molecular Medicine, Berlin-Buch, Germany.
SO TUMOUR BIOLOGY, (1998) 19 Suppl 1 88-99.
Journal code: TUB; 8409922. ISSN: 0289-5447.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199801
ED Entered STN: 19980130
Last Updated on STN: 19980130
Entered Medline: 19980121
AB The epithelial mucin MUC1 is heavily but differently glycosylated depending on the origin and developmental status of the tissue, which greatly influences the reactivity of monoclonal antibodies (MAbs). A partial characterization of their epitopes is possible by mild, carbohydrate-specific periodate oxidation of tissue sections prior to immunostaining. Using this strategy, we have evaluated 56 MAbs submitted to the ISOBM TD-4 (MUC1) Workshop. Paraffin sections from normal human small intestine, colon and breast were immunostained at different defined antibody concentrations either directly or after oxidation with 20 mM periodate at pH 5 for 30 min (PO). In addition, monolayers of T-47D **breast cancer** cells without PO **treatment** were examined in immunofluorescence. The array of observed reactivities allowed us to classify the MAbs as follows. Fourteen **antibodies** were found to detect **MUC1** largely independent of the degree of glycosylation, and are therefore classified as pan-**MUC1** MAbs (Group A). Twenty-four MAbs were nonreactive with one or more types of the examined epithelia, but became reactive after PO of the tissue sections. We have called these differentiation-dependent MUC1 MAbs (Group B). They might be especially valuable in histological tumour diagnosis. According to their differential staining behaviour towards untreated small intestine, colon, and breast tissue sections, we divided these MAbs into 4 subtypes (Group B1 through Group B4). A further group of six MAbs detected PO-sensitive carbohydrate epitopes (Group C). A seventh antibody apparently also belongs to Group C by immunohistological criteria, although its corresponding epitope was not PO-sensitive. Three further MAbs are still unclear in their specificity, and another 2 are not MUC1-specific (Group D). Six preparations were found nonreactive with the examined tissues; 4 of these were also negative with T-47D cells. Generally, a broad spectrum of different immunohistological patterns has emerged which appears to be widely independent of the type of epitope

(sequence versus conformational, length of sequence) and the relative affinities determined in vitro.

AB . . . directly or after oxidation with 20 mM periodate at pH 5 for 30 min (PO). In addition, monolayers of T-47D **breast cancer** cells without PO **treatment** were examined in immunofluorescence. The array of observed reactivities allowed us to classify the MAbs as follows. Fourteen **antibodies** were found to detect **MUC1** largely independent of the degree of glycosylation, and are therefore classified as pan-**MUC1** MAbs (Group A). Twenty-four MAbs were nonreactive with one or more types of the examined epithelia, but became reactive after. . .

L3 ANSWER 18 OF 21 MEDLINE
AN 96216551 MEDLINE
DN 96216551 PubMed ID: 8647622
TI Distinct sub-populations of carcinoma-associated MUC1 mucins as detected by the monoclonal antibody 9H8 and antibodies against the sialyl-Lewis a and sialyl-Lewis x epitopes in the circulation of **breast-cancer** patients.
AU Sikut R; Zhang K; Baeckstrom D; Hansson G C
CS Institute of Molecular and Cell Biology, University of Tartu, Estonia.
SO INTERNATIONAL JOURNAL OF CANCER, (1996 May 29) 66 (5) 617-23. Journal code: GQU; 0042124. ISSN: 0020-7136.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199607
ED Entered STN: 19960805
Last Updated on STN: 19960805
Entered Medline: 19960722
AB The cancer-associated epitope defined by the monoclonal antibody (MAb) 9H8 was shown to be closely related to the T antigen (Thomsen-Friedenreich antigen) by its sensitivity to 0-glycanase **treatment** of a mucin glycopeptide known to express this epitope. The reactivity with this glycopeptide increased upon neuraminiclase **treatment**, and among several MAbs tested for ability to block binding of the 9H8 antibody, the one specific for the T antigen was the most efficient. Out of 41 serum samples from **breast-cancer** patients, 11 showed elevated levels of the 9H8 epitope, and several sera also showed elevated levels of the cancer-associated carbohydrate epitopes sialyl-Lewis a and sialyl-Lewis x. By the use of **antibodies** specific for the **MUC1** apoprotein (Ma552 and HMFG-2) it could be shown that these epitopes were attached to the **MUC1** apoprotein in at least 4 of the cases. By combining antibodies specific to 9H8, sialyl-Lewis a and sialyl-Lewis x in catcher and tracer positions in several types of immunofluorometric assays, it was shown that the 9H8 epitope was rarely co-expressed with sialyl-Lewis a or sialyl-Lewis x epitopes an the same molecule, though all were expressed on MUC1 mucins. In fact, they can be considered as mutually exclusive epitopes, suggesting that these sera contained different populations of MUC1 mucins distinguishable by different sets of oligosaccharides. The existence of mutually exclusive carbohydrate epitopes on different MUC1 mucins in one and the same patient should be taken into account when designing immunoassays exploiting MUC1-reactive antibodies.
TI . . . detected by the monoclonal antibody 9H8 and antibodies against the sialyl-Lewis a and sialyl-Lewis x epitopes in the circulation of **breast-cancer** patients.
AB . . . antibody (MAb) 9H8 was shown to be closely related to the T antigen (Thomsen-Friedenreich antigen) by its sensitivity to 0-glycanase **treatment** of a mucin glycopeptide known to express this epitope. The reactivity with this glycopeptide increased upon neuraminiclase **treatment**, and among several MAbs tested for ability to block binding of the 9H8 antibody, the one specific for the T antigen was the

L13 ANSWER 14 OF 15 CABA COPYRIGHT 2000 CABI
AN 92:111801 CABA
DN 920455329
TI Studies of Muc-1 mucin expression and polarity in the mouse mammary gland demonstrate developmental regulation of Muc-1 glycosylation and establish the hormonal basis for mRNA expression
AU Parry, G.; Li, J.; Stubbs, J.; Bissell, M. J.; Schmidhauser, C.; Spicer, A. P.; Gendler, S. J.
CS Cell and Molecular Biology Division, Lawrence Berkeley Laboratory, University of California, Berkeley, CA 94720, USA.
SO Journal of Cell Science, (1992) Vol. 101, No. 1, pp. 191-199. 24 ref. ISSN: 0021-9533
DT Journal
LA English
AB Muc-1 is a major mucin glycoprotein expressed on the surface of mammary epithelial cells (MEC). It has attracted considerable attention as it is expressed in an aberrant form on many **breast tumour** cells. Studies using a recently obtained cDNA probe of **Muc-1** expression during lactogenic development in the mouse are described. Northern-blot analysis demonstrated that Muc-1 is expressed at all stages of lactogenic development but its levels are increased very significantly during mid-pregnancy and into lactation. The basis of this was examined using CID-9 MEC cultures. It was found that in the presence of insulin Muc-1 mRNA levels were increased by both hydrocortisone and prolactin, with the combination of the 3 hormones supporting max. expression. Muc-1 mRNA levels were also modulated by culturing cells on a basement membrane-like extracellular matrix that promoted mRNA levels 5- to 10-fold above levels in cells cultured on plastic tissue dishes. Immunocytochemical studies using monoclonal **antibodies** to carbohydrate epitopes on **Muc-1** demonstrated that, while **Muc-1** was found at all developmental stages, it became increasingly sialylated during the course of pregnancy and into lactation. Additionally, it was found that, while Muc-1 is tightly polarized to the apical surface of the epithelium of lactating and pregnant mice, it exhibited a less-polarized distribution on a small proportion of ductal cells in virgin mice. It is concluded that the expression of Muc-1 is regulated at several different levels and by a number of different factors, and it is speculated that this may reflect different functional roles for Muc-1 at different stages of mammary development.
CC LL600 Animal Physiology and Biochemistry (Excluding Nutrition)
BT Muridae; rodents; mammals; vertebrates; Chordata; animals
CT Glycoproteins; gene expression; mammary glands; epithelium
ORGN mice

L3 ANSWER 18 OF 26 CANCERLIT
AN 95604734 CANCERLIT
DN 95604734
TI Efficacy of immunotoxins as therapy for human leptomeningeal CNS tumors in
nude rats (Meeting abstract).
AU Fodstad O; Myklebust A T; Juell S; Godal A
CS Dept. Tumor Biology, The Norwegian Radium Hosp., Oslo, Norway.
SO Proc Annu Meet Am Assoc Cancer Res, (1994). Vol. 35, pp. A3049.
ISSN: 0197-016X.
DT (MEETING ABSTRACTS)
FS ICDB; L
LA English
EM 199503
AB Models for secondary spread of human tumors to the CNS of nude rats were developed. The malignant cells were injected into the cisterna magna of the recipient animals and deposited directly into the cerebrospinal fluid.

Growth of melanoma, lymphoma, **lung** and breast cancer cells presented as multiple small leptomeningeal tumors, particularly on the surface of the cerebellum. The tumors manifested themselves with clinical symptoms of CNS involvement within 10-40 days, with reproducible latency times specific for each cell line. Immunotoxins consisting of Pseudomonas exotoxin (PE) or an abrin variant conjugated to transferrin, or to tumor type-associated monoclonal **antibodies**, showed differential activities against the various tumors. In a small cell **lung** cancer model, **MOC31**-PE delayed the onset of symptoms up to 70% compared to the control group when injected with glycerol. Similar activity was seen with 9.2.27-PE in the LOX melanoma model, whereas the highest activity (180%) was seen with an anti-EGFr-PE conjugate, with results far better than reported for other therapeutic approaches in similar models. Immunotoxins may, therefore, represent an interesting alternative in the clinical management of patients with leptomeningeal

ANSWER 13 OF 26 SCISEARCH COPYRIGHT 2000 ISI (R) DUPLICATE 5
AN 97:297098 SCISEARCH
GA The Genuine Article (R) Number: WR929
TI A novel immunotoxin recognising the epithelial glycoprotein-2 has potent antitumoural activity on chemotherapy-resistant **lung** cancer
AU Zimmermann S; Wels W; Froesch B A; Gerstmayer B; Stahel R A; ZangemeisterWittke U (Reprint)
CS UNIV ZURICH HOSP, DIV ONCOL, CH-8044 ZURICH, SWITZERLAND (Reprint); UNIV ZURICH HOSP, DIV ONCOL, CH-8044 ZURICH, SWITZERLAND; INST EXPT CANC RES, TUMOUR BIOL CTR, D-79106 FREIBURG, GERMANY
CYA SWITZERLAND; GERMANY
SO CANCER IMMUNOLOGY IMMUNOTHERAPY, (MAR 1997) Vol. 44, No. 1, pp. 1-9. Publisher: SPRINGER VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010. ISSN: 0340-7004.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 35
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Resistance to chemotherapy is a major cause for failure in the treatment of **lung** cancer. Compared to conventional cytotoxic drugs, immunotoxins act by different mechanisms and thus might be promising for the treatment of chemoresistant cancer. The monoclonal **antibody MOC31** recognises the epithelial glycoprotein-2 (EGP-2), a cell-surface antigen associated with small-cell **lung** cancer (SCLC) and a major fraction of **lung** adenocarcinomas. An immunotoxin composed of **MOC31** and a recombinant form of Pseudomonas exotoxin A lacking the cell-binding domain (ETA(252-613)) was prepared, and its effect on **lung** cancer cell lines examined. **MOC31**-ETA(252-613) was selectively cytotoxic to EGP-2-positive SCLC and adenocarcinoma cell lines inhibiting proliferation by 50% at concentrations ranging from 0.01 nM to 0.3 nM. Moreover, the immunotoxin reduced the number of clonogenic tumour cells from cultures by factors of 10(4) and 10(5) during a 24-h and a 3-week exposure respectively. In athymic mice, the immunotoxin, which revealed a serum half-life of approximately 4 h, caused substantial regression of small (40 mm(3)) chemoresistant tumour xenografts and significantly delayed the growth of larger tumours (120 mm(3)). This finding indicates that **MOC31** -ETA(252-613) may be useful for the treatment of **lung** cancer in the setting of chemoresistant minimal residual disease.

L

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=> d his

     (FILE 'HOME' ENTERED AT 09:02:29 ON 21 MAR 2002)

     FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, LIFESCI, WPIDS, USPATFULL' ENTERED
     AT 09:03:54 ON 21 MAR 2002
L1           15 S EGP-2(25W)LOCAL?
L2            5 DUP REM L1 (10 DUPLICATES REMOVED)
L3           23 S EGP-2(25W)NORMAL
L4            6 DUP REM L3 (17 DUPLICATES REMOVED)
L5           40 S EGP-2(25W)EPITHEL?
L6           19 DUP REM L5 (21 DUPLICATES REMOVED)
```

File U

L3 ANSWER 20 OF 21 CAPLUS COPYRIGHT 2002 ACS
AN 1995:508513 CAPLUS
DN 122:288268
TI The immunogenicity of MUC1 peptides and fusion protein
AU Apostolopoulos, V.; Pietersz, G. A.; Xing, P.-X.; Lees, C. J.; Michael, M.; Bishop, J.; McKenzie, I. F. C.
CS Austin Research Institute, Austin Hospital, Studley Road, Heidelberg, Vic., 3084, Australia
SO Cancer Lett. (Shannon, Irel.) (1995), 90(1), 21-6
CODEN: CALEDQ; ISSN: 0304-3835
DT Journal; General Review
LA English
AB A review and discussion with 22 refs. Mucin1 (MUC1) is highly expressed in **breast cancer**, has an ubiquitous distribution and, due to altered glycosylation, peptides within the VNTR are exposed. These peptides are the target for anti-MUC1 antibodies, which give a differential reaction on cancer compared with normal tissue. The amino acids, APDTR or adjacent amino acids, are highly immunogenic in mice for antibody prodn. (after immunization with either **breast cancer** cells, human milk fat globule (HMFG) or the VNTR peptide). In addn., human studies show that this region of the MUC1 VNTR functions as target epitopes for cytotoxic T cells. We have performed preclin. and clin. studies to examine the immune responses to MUC1 in mice and humans: (a) MUC1+ 3T3 or P815+ 3T3 cells in syngeneic mice are rejected, with the generation of both cytotoxic T lymphocyte (CTL) and DTH responses and a weak antibody response; this type of immunity gives rise to total resistance to re-challenge with high doses of these tumors; (b) immunization with peptides (VNTR .times. 2), a fusion protein (VNTR.times.5), or HMFG leads to no CTLs, DTH, good antibody prodn. and weak tumor protection (to 106 cells, but not 5.times.106 cells) (possibly a TH2 type response); (c) immunization with mannan-fusion protein (MFP) gives rise to good protection (resistance to 50.times.106 cells), CTL and DTH responses and weak antibody responses (possibly a TH1 type response, similar in magnitude to that obtained after tumor rejection); (d) established tumors can be rapidly rejected by delayed **treatment** of MFP; (e) the CTL responses are MHC restricted (in contrast to the human studies); (f) APDTR appears not to be the T cell reactive epitope in mice. On the basis of these findings, two clin. trials are in progress: (a) VNTR .times. 2 (diphtheria toxoid) which gives rise to some T cell proliferation, DTH and antibody responses in some patients and (b) an MFP trial. The ability to alter the immune response towards cellular immunity with mannan or to humoral immunity with peptides, allows the immune response to be selectively manipulated.
AB A review and discussion with 22 refs. Mucin1 (MUC1) is highly expressed in **breast cancer**, has an ubiquitous distribution and, due to altered glycosylation, peptides within the VNTR are exposed. These peptides are the target for anti-MUC1 antibodies, which give a differential reaction on cancer compared with normal tissue. The amino acids, APDTR or adjacent amino acids, are highly immunogenic in mice for antibody prodn. (after immunization with either **breast cancer** cells, human milk fat globule (HMFG) or the VNTR peptide). In addn., human studies show that this region of the MUC1 VNTR functions as target epitopes for cytotoxic T cells. We have performed preclin. and clin. studies to examine the immune responses to MUC1 in mice and humans: (a) MUC1+ 3T3 or P815+ 3T3 cells in syngeneic mice are rejected, with the generation of both cytotoxic T lymphocyte (CTL) and DTH responses and a weak antibody response; this type of immunity gives rise to total resistance to re-challenge with high doses of these tumors; (b) immunization with peptides (VNTR .times. 2), a fusion protein (VNTR.times.5), or HMFG leads to no CTLs, DTH, good antibody prodn. and weak tumor protection (to 106 cells, but not 5.times.106 cells) (possibly a TH2 type response); (c) immunization with mannan-fusion protein (MFP) gives rise to good protection (resistance to 50.times.106 cells), CTL and

evaluation of bispecific scFvs and scFv-based fusion proteins. An important feature of this vector is the presence of two multiple cloning sites (MCS) separated by an in frame linker sequence. The first MCS was specifically designed to contain unique SfiI and NotI restriction enzyme sites that can be used for directional and in frame insertion of scFvs (or potentially any molecule) selected from established phage-display systems. Using this new vector, a functional bs-(scFv)(2) (2C11-MOC31) was constructed for retargeted T-cell cytotoxicity towards **EGP2** positive **tumor** cells. The vector was also used for grafting of a number of promising biological effector principles onto scFv MOC31, including the prodrug converting enzyme cytosine deaminase, the anti-angiogenic factor angiostatin, and the thrombogenic molecule tissue factor. We aimed at producing biologically active fusion proteins by directing them through the endoplasmic reticulum-based protein folding machinery of eukaryotic cells (COS-7) using a kappa light chain leader, thereby taking advantage of the associated quality control mechanisms that allow only fully folded and processed fusion proteins to be secreted into the medium. Supernatants derived from fusion protein transfected COS-7 cells, which were transiently transfected at low transfection rates, were directly assayed for the biological and/or targeting activity of the excreted fusion proteins without any prior purification steps. This procedure might help to identify those fusion proteins that have favourable characteristics like stability and biological activity in the presence of serum and at low protein concentrations. Targeted delivery of all effector principles was subsequently assessed in an in vitro model system. The method we devised is both rapid and versatile and can be useful to construct and identify series of new chimeric proteins with enhanced therapeutic potential in human cancer therapy.

File V

L7 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2002 ACS
AN 2001:401949 CAPLUS
DN 135:165763
TI The epithelial glycoprotein 2 (EGP-2) promoter-driven epithelial-specific expression of EGP-2 in transgenic mice: a new model to study carcinoma-directed immunotherapy
AU McLaughlin, Pamela M. J.; Harmsen, Martin C.; Dokter, Wim H. A.; Kroesen, Bart-Jan; Van der Molen, Henk; Brinker, Marja G. L.; Hollema, Harry; Ruiters, Marcel H. J.; Buys, Charles H. C. M.; De Leij, Lou F. M. H.
CS Department of Pathology and Laboratory Medicine, section of Medical Biology, University Hospital Groningen, Groningen, 9713 GZ, Neth.
SO Cancer Research (2001), 61(10), 4105-4111
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
AB The human pancarcinoma-assocd. epithelial glycoprotein-2 (EGP-2), a Mr 38,000 transmembrane antigen also known as 17-1A or Ep-CAM, is commonly used for targeted immunotherapy of carcinomas because it is strongly expressed by most carcinomas. EGP-2 is, however, also expressed in most normal epithelia. To evaluate anti-EGP-2-directed treatment-assocd. effects on tumors and on EGP-2-pos. normal tissue, we generated EGP-2-expressing transgenic mice. A 55-kb DNA fragment consisting of the 14-kb genomic coding sequence of the human EGP-2 gene with .apprx.10-kb-upstream and .apprx.31-kb-downstream sequences was isolated and used to direct EGP-2 expression in an epithelium-specific manner. In the EGP-2 transgenic mice, EGP-2 appeared to be specifically expressed in all of those epithelial tissues that also express EGP-2 in humans, whereas all of the other tissues were neg. The specific in vivo localization of the i.v. administered anti-EGP-2 monoclonal antibody MOC31 was studied in EGP-2-pos. and -neg. tumors induced s.c. in this EGP-2 transgenic mouse model. Immunohistochem. anal. showed specific localization of MOC31 in the EGP-2-pos. tumors but not in the EGP-2-neg. tumors. No anti-EGP-2 monoclonal antibody localization was obsd. in any of the EGP-2-pos. normal mouse tissues, which indicated a limited in vivo accessibility. In conclusion, an EGP-2 transgenic mouse model has been generated that expresses the EGP-2 antigen as in humans and, therefore, can serve as a model to evaluate the efficacy and safety of a variety of anti-EGP-2-based immunotherapeutic modalities in both tumors and normal tissue.
RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

DUPLICATE 1

L7 ANSWER 2 OF 5 MEDLINE
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DN 20192069 PubMed ID: 10725458
TI A rapid and versatile method for harnessing scFv antibody fragments with various biological effector functions.
AU Helfrich W; Haisma H J; Magdolen V; Luther T; Bom V J; Westra J; van der Hoeven R; Kroesen B J; Molema G; de Leij L
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AB A versatile expression vector is described for the rapid construction and